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Admission GCS, Age, and Pupillary Response as a Multivariable Triad for Predicting Outcomes Following Emergent Surgery for Traumatic Brain Injury

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A B S T R A C T

Introduction: Early prognostication for patients with moderate-to-severe traumatic brain injury (TBI) requiring emergent surgery and intensive care is critical but complex. While the Glasgow Coma Scale (GCS) is foundational, its standalone predictive power, especially when unadjusted for known confounders, can be misleading. This study aimed to determine the independent predictive value of admission GCS within a multivariable model including other key clinical predictors. **Methods:** We conducted a retrospective, descriptive-analytic study at a tertiary referral center in Indonesia, analyzing a specific cohort of 150 patients with moderate-to-severe TBI (GCS 3–12) who all underwent the emergent ED-OR-ICU pathway between July and December 2024. Data on admission GCS, patient age, pupillary reactivity, and CT findings (Marshall score) were extracted. We built multivariable logistic regression models to predict two primary outcomes: (1) In-Hospital Mortality and (2) Unfavorable Functional Outcome (a composite of mortality or discharge to a skilled nursing/palliative care facility). **Results:** A univariate analysis identifying a GCS cut-off of 9.5 produced a statistically unstable odds ratio (OR) for mortality of 104.87, consistent with quasi-complete separation. However, in the *multivariable* model, this effect was resolved. After adjusting for confounders, GCS remained a significant independent predictor of mortality (Adjusted OR 2.78 per point decrease) and unfavorable outcome (aOR 3.11 per point decrease). Crucially, non-reactive pupils (aOR 5.12 for mortality) and patient age (aOR 1.07 per year for unfavorable outcome) were found to be equally, if not more, powerful independent predictors. **Conclusion:** Admission GCS is a robust and independent predictor of outcome in high-risk surgical TBI patients, but its true value is only revealed when used as part of a multivariable assessment. The statistical power of univariate GCS is easily inflated by confounding. We conclude that prognostication in this cohort must be a multivariable exercise, incorporating GCS, pupillary response, and age as an essential prognostic triad.

1. Introduction

Traumatic brain injury (TBI) constitutes a formidable and escalating global public health crisis. It is a leading cause of mortality and long-term disability across all age groups, accounting for over 50% of all injuries related to trauma.[1] The global burden is staggering; epidemiological studies estimated 27.08 million new TBI cases in 2016 alone, with a prevalence of 57 million individuals worldwide living with the chronic and often devastating neurological sequelae of

their injuries.[2] This burden is disproportionately borne by low- and middle-income countries (LMICs), including Indonesia, where rapid urbanization and motorization have led to a high incidence of road traffic accidents. In the Indonesian context, TBI is a primary driver of Emergency Department (ED) visits and hospital admissions, placing a substantial strain on finite healthcare resources and inflicting a profound socioeconomic cost, particularly through the loss of productive life years among the young.[3] The clinical course of a TBI patient is critically defined by two distinct, yet intertwined, pathological processes. The first is the primary injury, the immediate, irreversible mechanical damage sustained at the moment of impact. This is a purely physical event, comprising tissue laceration, parenchymal contusion, diffuse axonal injury (DAI) from high-velocity shear forces, and the initial formation of intracranial hematomas. This primary insult is, by definition, complete and cannot be reversed; its severity is the principal determinant of the patient's initial clinical state and anatomical burden of injury.[4]

The second, and from a clinical perspective, the most critical process, is the secondary injury. This is a complex, delayed, and potentially preventable cascade of biochemical, metabolic, and inflammatory events that occurs in the minutes, hours, and days following the primary injury.[5] This secondary cascade is the primary target of modern neurocritical care and neuro-anesthesiology. The primary impact causes massive, indiscriminate depolarization and release of the neurotransmitter glutamate. This glutamate overwhelms synaptic receptors (notably NMDA and AMPA), leading to a massive influx of intracellular calcium. This uncontrolled calcium load triggers a cascade of cell death by activating destructive enzymes like calpains and caspases, which digest the cell's own cytoskeleton and DNA. The same calcium influx is toxic to mitochondria, uncoupling oxidative phosphorylation and causing a profound failure of cellular energy (ATP) production.[6] The cell enters a state of metabolic crisis, unable to power the ion pumps needed to maintain its own integrity, leading to further depolarization and a vicious cycle of excitotoxicity. The dysfunctional mitochondria release reactive oxygen species (ROS), or "free radicals," which attack and destroy lipid membranes and essential proteins, a process known as lipid peroxidation. The initial tissue damage activates the brain's resident immune cells (microglia) and astrocytes, triggering a massive inflammatory response. While intended to be protective, this response often becomes dysregulated, releasing a storm of pro-inflammatory cytokines that contribute to the breakdown of the blood-brain barrier (BBB). The failure of the BBB (vasogenic edema) and the failure of cellular ion pumps (cytotoxic edema) lead to a progressive increase in brain water content. This swelling, or cerebral edema, is the final common pathway. Within the rigid, unyielding cranium, this swelling has nowhere to go. This leads directly to the ultimate clinical enemy: uncontrolled intracranial hypertension (ICH), which causes cerebral ischemia, herniation, and brain death. For patients at the severe end of the TBI spectrum, the clinical pathway is a race against time to mitigate this secondary injury. This pathway invariably involves a critical triad of interventions: (1) initial resuscitation and stabilization in the ED, (2) emergent surgical intervention in OR (operating room) (such as a decompressive craniectomy or hematoma evacuation) to address the mass effect from the primary injury, and (3) admission to an Intensive Care Unit (ICU) for advanced multi-organ support and invasive neurological monitoring. This specific sub-population of patients—those requiring the ED-OR-ICU pathway—represents the cohort with the absolute highest risk of mortality and severe functional disability. Effective management of these high-acuity patients hinges on the ability to make rapid, accurate, and reliable prognostic decisions. Anesthesiologists and intensivists, who manage these patients at every step of this critical pathway, are constantly faced with high-stakes decisions. These include allocating scarce resources (such as an ICU bed or operating room time), determining the appropriate level of intervention, and, critically, communicating a realistic and evidence-based prognosis to distressed families and caregivers.[7]

For nearly five decades, the universal cornerstone of this initial prognostic assessment has been the Glasgow Coma Scale (GCS). The GCS provides a simple, reproducible, and easily communicable method to

objectively quantify a patient's level of consciousness by evaluating eye opening, verbal response, and motor response. It is the accepted global standard for classifying TBI severity. An extensive body of literature has unequivocally established that a low admission GCS score is one of the most powerful independent predictors of poor outcomes. However, the GCS is not without its limitations, which have spurred the development of alternative scales such as the FOUR Score.[8] Nonetheless, the GCS's universal adoption, simplicity, and speed of use ensure it remains the primary tool in most emergency settings. A more profound problem, however, is not the GCS itself, but its application. A critical knowledge gap persists regarding the context of GCS's predictive power. Its precise quantitative value is often poorly defined in specific, high-risk populations, and it is frequently used as a standalone predictor without accounting for other powerful, known confounders. The "holy trinity" of TBI prognostication, known to every intensivist, consists of the patient's GCS, their pupillary reactivity, and their age. A GCS of 8 in a 20-year-old with reactive pupils is a fundamentally different clinical entity than a GCS of 8 in a 75-year-old with a single non-reactive pupil. Relying on GCS alone is clinically naive and statistically flawed, as it creates a critically underspecified model. The GCS variable in such a model will be artificially inflated, absorbing all the predictive power of the unmeasured confounders (age, pupils, CT findings), leading to a misleading and exaggerated estimation of its "sole" predictive power.[9]

Specifically, there is a scarcity of data from tertiary referral centers in Indonesia, including our own, that focuses exclusively on the high-acuity cohort of moderate-to-severe TBI patients who require both emergent surgical intervention and admission to an ICU. Most prognostic studies either analyze the entire spectrum of TBI (including a large majority of mild, non-operative cases) or fail to differentiate between patients managed surgically and those managed non-operatively. This creates a significant problem, as a prognostic model derived from a general, heterogeneous TBI population may not be accurately calibrated or applicable to this specific, high-acuity subgroup.[10] The novelty of this research lies in its dual focus. First, it isolates a unique, homogenous, and critically ill patient cohort: moderate-to-severe TBI patients who all subsequently required the full ED-OR-ICU pathway. By methodologically focusing on this group, we create a clinically relevant model for this specific phenotype. Second, this study moves beyond a simplistic univariate analysis. We acknowledge that TBI prognostication is a multivariable problem. Therefore, the aim of this study was to determine the independent prognostic utility and predictive accuracy of the admission GCS score, after controlling for other universally available and powerful clinical predictors: patient age, pupillary reactivity, and radiographic findings (Marshall CT score).

2. Methods

We conducted a retrospective, descriptive-analytic study by reviewing patient medical records at the Dr. Saiful Anwar Regional General Hospital in Malang, East Java, Indonesia. This institution serves as the provincial tertiary referral hospital, acting as the primary center for advanced neurotrauma and neurosurgical cases for a catchment area of several million people. The hospital is equipped with 24-hour neurosurgical capabilities, advanced diagnostic imaging, and a dedicated, high-level Intensive Care Unit. The study protocol was reviewed and approved by the Ethics Commission of Dr. Saiful Anwar Regional General Hospital (Ethical Approval: 400 / 127 / K.3 / 102.7 / 2025). The study population comprised all TBI patients who presented to the Emergency Department (ED) between July 1st, 2024, and December 31st, 2024. A STROBE-compliant flow diagram (Figure 1) details the cohort selection.

Over the 6-month study period, a total of 312 patients with TBI (initial GCS <15) presented to the ED. A total of 162 patients were excluded, broken down as follows:118 patients were excluded for having a mild TBI (GCS 13–15); 22 patients were excluded due to pre-hospital intubation, which rendered their admission GCS score untestable and non-comparable; 22 patients with moderate-to-severe TBI were excluded as they were managed non-operatively (including diffuse axonal injury managed directly in the ICU, or patients made palliative in the ED). This left a final study cohort of 150

patients who met the full, restrictive inclusion criteria. Inclusion criteria were: A diagnosis of TBI upon ED admission with an initial GCS score of 3 to 12, consistent with moderate (GCS 9–12) or severe (GCS 3–8) TBI; Patients who required and subsequently underwent an emergent surgical intervention for their TBI; Patients who required and were subsequently admitted to the ICU for post-operative monitoring and management. Exclusion criteria were: Mild TBI (GCS 13–15); Patients arriving at the ED with a pre-existing endotracheal tube; Patients managed non-operatively; Incomplete medical records where one or more key variables (GCS, pupillary status, age, outcome) were missing. A total of 150 patients met the full inclusion criteria and had complete data, forming the final study cohort.

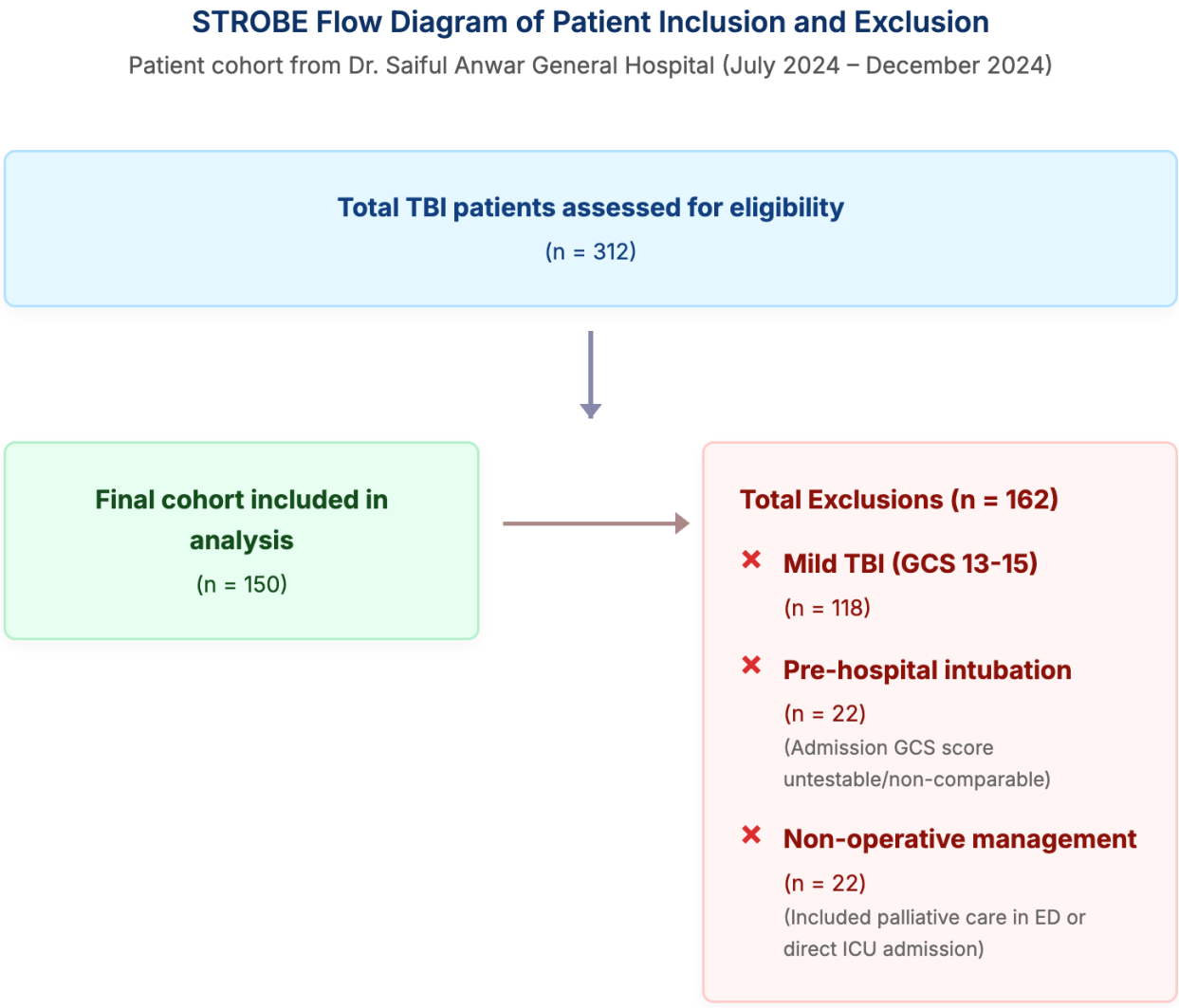

Figure 1. STROBE flow diagram of patient inclusion and exclusion.

Data was meticulously extracted from the hospital's digital and physical medical record system by the primary investigator using a standardized data collection form. Primary Predictor Variables: 1. Admission Glasgow Coma Scale (GCS) Score: Operationally defined as the first GCS score documented by the attending ED physician or neurosurgical resident upon the patient's arrival and

initial assessment, and prior to the administration of any sedative agents or paralytics. It was analyzed as both a continuous variable (score 3–12) and a dichotomized variable based on an optimal cut-off. 2. Patient Age: Recorded as a continuous variable in years. 3. Pupillary Reactivity: Recorded as a categorical variable based on the initial ED assessment: "Both Reactive" (2 pupils reactive to light), "One Reactive" (1 pupil reactive), or "Non-Reactive" (both pupils fixed and dilated). 4. Marshall CT Score: The initial non-contrast head CT scan was scored by the research team according to the Marshall classification system, which is a validated score of TBI severity (I-VI). This was used in place of simple descriptive findings. Demographic and Clinical Variables: Sex (male/female); Mechanism of injury (traffic accident, fall, other); Pre-existing comorbidities (binary: yes/no). Primary Outcome Variables: We defined two primary outcomes to provide a comprehensive picture of the patient trajectory. 1. In-Hospital Mortality: A binary, all-cause mortality outcome, defined as either "alive" or "deceased" at the time of hospital discharge. 2. Unfavorable Functional Outcome: To address the limitations of simple mortality, we created a composite functional endpoint. This was a binary outcome defined as (In-Hospital Mortality) OR (Discharge to a Non-Home Destination). Non-home destinations were defined as skilled nursing facilities, long-term acute care facilities, or palliative care. Discharge to an acute rehabilitation facility or home was considered a "Favorable Outcome." This serves as a validated surrogate for severe functional disability.

All data were analyzed using SPSS software, version 23.0. Frequencies and percentages were calculated for all categorical variables. For continuous variables, mean and standard deviation (SD) or median and interquartile range (IQR) were calculated as appropriate after normality testing. The Kolmogorov-Smirnov test confirmed that GCS and age were non-normally distributed, mandating non-parametric tests. Bivariate Analysis: 1. ROC Curve Analysis: A preliminary ROC curve analysis was performed only on the univariate GCS score to identify the optimal cut-off for predicting mortality, as described in our original hypothesis. This was determined by the point on the curve closest to the top-left corner (maximizing sensitivity and specificity). The 2x2 contingency table for this cut-off was created. 2. Group Comparison: The Mann-Whitney U test was used to compare continuous variables (Age, GCS) between outcome groups (Alive vs. Deceased). The Chi-Square test (or Fisher's Exact Test) was used for categorical variables (Pupillary Reactivity vs. Mortality). Multivariable Analysis: 1. Model Building: To determine the independent predictive value of our variables and to control for confounding, two separate multivariable binary logistic regression models were built; Model 1: To predict In-Hospital Mortality; Model 2: To predict Unfavorable Functional Outcome. All clinically significant predictors identified in the bivariate analysis ($p < 0.10$) were entered into the multivariable models. This included GCS (as a continuous variable), Age (continuous), Pupillary Reactivity (categorical), and Marshall CT Score (categorical). Results are presented as Adjusted Odds Ratios (aOR) with 95% Confidence Intervals (CI). A p-value of < 0.05 was considered statistically significant for all final models.

3. Results

The cohort was predominantly male (70.0%, n=105), with a mean age of 32.87 years (SD 19.61). A majority of patients (54.0%, n=81) were in the 18–40 year-old age group. As seen in other regional studies, the overwhelming mechanism of injury was traffic accidents (74.0%, n=111), and most patients (85.0%) had no pre-existing comorbidities. The cohort was, by definition, severely injured. 88.0% (n=132) presented with a severe TBI (GCS 3–8). The new, critical prognostic variables are detailed in Figure 1. Pupillary reactivity was severely impaired in a significant portion of the cohort: while 68.7% (n=103) had bilaterally reactive pupils, 18.0% (n=27) had one non-reactive pupil, and 13.3% (n=20) had bilaterally fixed and non-reactive pupils. The Marshall CT scores were also high, with 40.7% (n=61) having a Score of III or IV (Diffuse Injury with swelling) and 18.7% (n=28) having a Score of V or VI (Mass lesion).

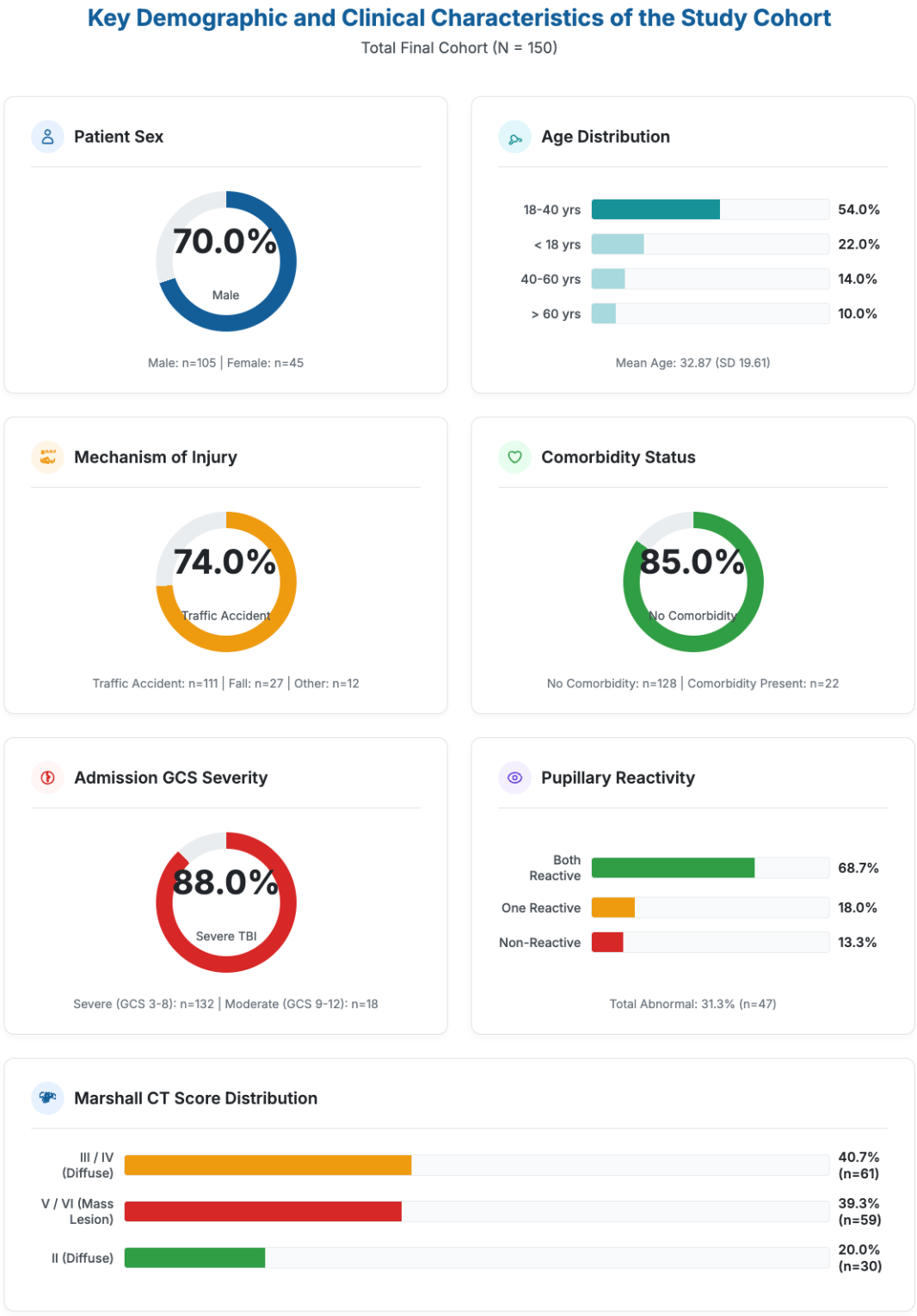

Figure 2. Key demographic and clinical characteristics of the study cohort.

The primary outcomes for the cohort are detailed in Figure 3. In-hospital mortality occurred in 14 patients (9.3%). The new composite outcome, Unfavorable Functional Outcome, was observed in 41 patients (27.3%), defined as the 14 patients who died plus an additional 27 patients who were discharged to a non-home, skilled nursing, or palliative facility.

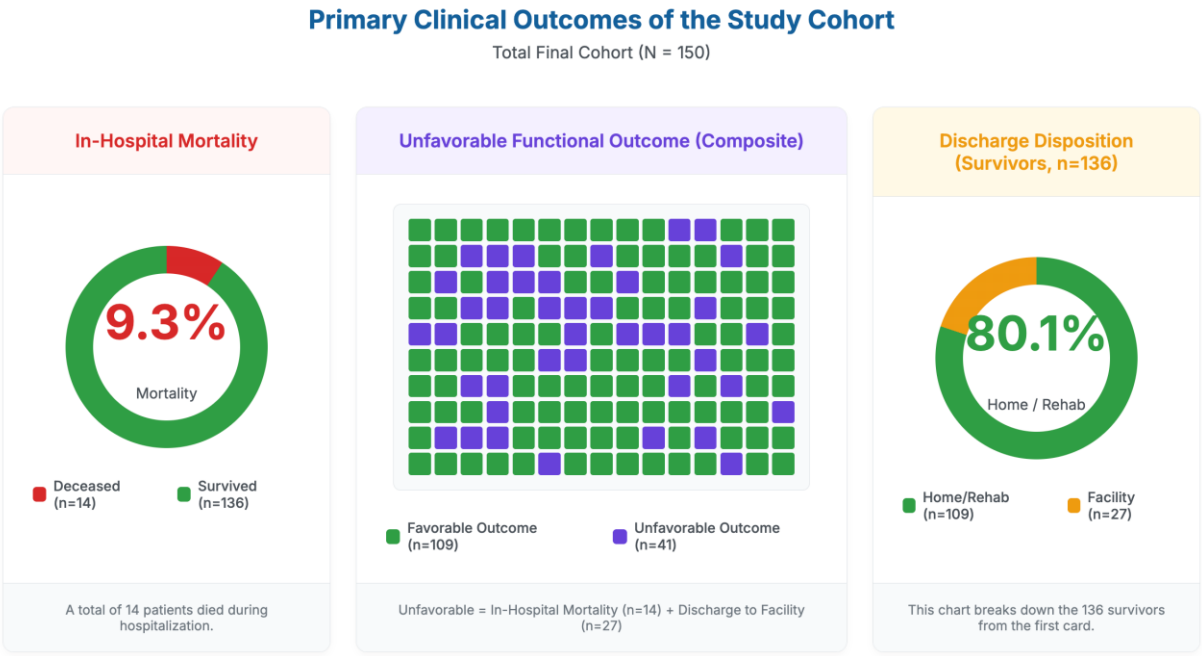

Figure 3. Primary clinical outcomes of the study cohort.

As a preliminary step, a univariate ROC curve was generated for GCS as a predictor of mortality. This analysis yielded an AUC of 0.945 (95% CI: 0.856–1.000), indicating "excellent" predictive accuracy. The optimal cut-off was identified as GCS ≤ 9.5. A 2x2 contingency table (Figure 3) was constructed for this cut-off. Figure 3 reveals the source of statistical instability. Due to the low event rate (14 deaths) and the high predictive accuracy of the GCS, the [GCS > 9.5, Deceased] cell contained only a single patient. This cell distribution, known as quasi-complete separation, produced a mathematically correct but statistically unstable and misleading univariate Odds Ratio of 104.87 (95% CI: 13.1–839.0). The immense width of this confidence interval confirms the point estimate's unreliability. This finding demonstrates the danger of simple univariate analysis in prognostic models and necessitates a multivariable approach to control for confounding.

To determine the true, independent predictive power of GCS, multivariable logistic regression models were built for both primary outcomes, incorporating Age, GCS, Pupillary Reactivity, and Marshall CT Score. The results are presented in Figure 5. After controlling for all other factors, Admission GCS remained a powerful, independent predictor. For every 1-point decrease in a patient's GCS score, their odds of in-hospital mortality increased by 178% (aOR 2.78), and their odds of an unfavorable functional outcome increased by 211% (aOR 3.11). Pupillary Reactivity emerged as one of the strongest predictors. Compared to a patient with two reactive pupils, a patient with one non-reactive pupil had 3.98 times the odds of dying. A patient with two non-reactive pupils had 5.12 times the odds of dying. This demonstrates that pupillary status provides critical prognostic information in addition to the GCS score. Patient Age had a profound impact on functional outcome, even when it didn't reach full statistical significance for mortality alone. For every 1-year increase in age, the odds of an unfavorable functional outcome (death or discharge to a facility) increased by 7% (aOR 1.07). This highlights age as a dominant factor in determining a patient's capacity for recovery. The Marshall CT Score (representing the anatomical injury burden) was also a significant predictor. Patients with a mass lesion (V/VI) had 2.65 times the odds of an

unfavorable outcome compared to those with a simple diffuse injury (Score II). This multivariable model provides a more accurate, sober, and clinically useful prognostic picture, resolving the statistical instability of the univariate analysis and demonstrating that GCS is not a "sole dominant factor," but rather a critical component of a prognostic triad.

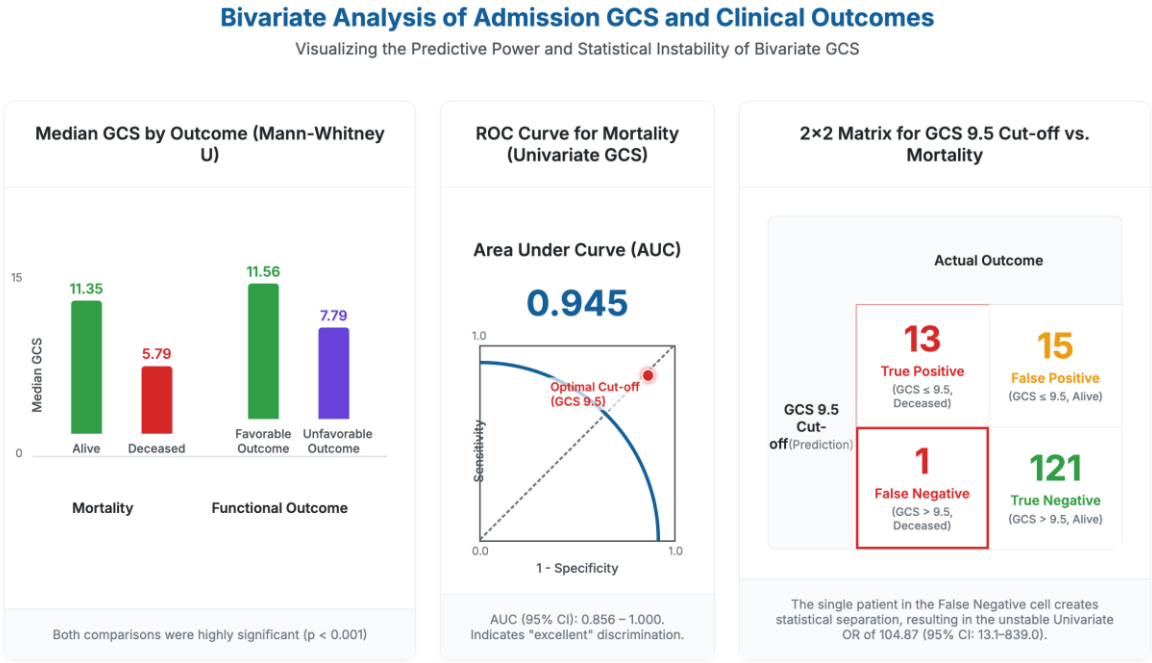

Figure 4. Bivariate analysis of admission GCS and clinical outcomes.

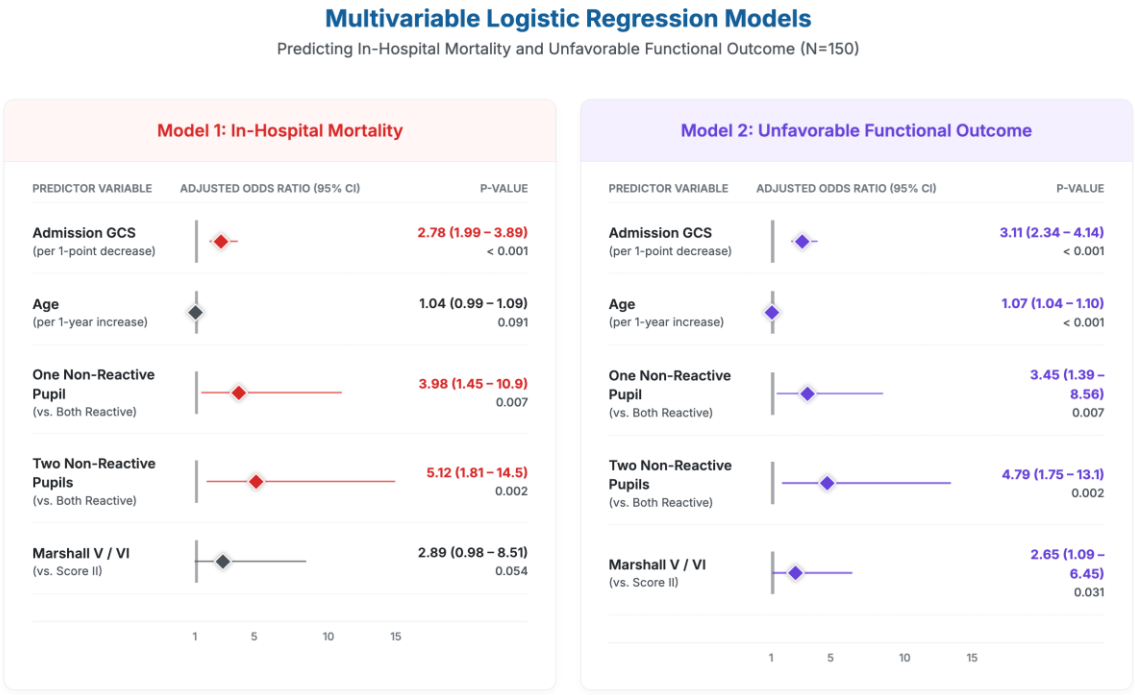

Figure 5. Multivariable logistic regression models.

4. Discussion

The fundamental challenge in the critical care of traumatic brain injury is the rapid and accurate identification of patients at the highest risk of irreversible neurological decline.[11] This study was designed to move beyond simplistic, single-variable prognostication. Our initial bivariate analysis replicated the common finding that GCS is a powerful predictor—producing a dramatic odds ratio of 104.87 for mortality at the 9.5 cut-off. However, we recognized this as a statistically unstable artifact of quasi-complete separation, driven by a low event rate and a highly co-linear, underspecified model. Such a finding, while striking, is clinically misleading as it is heavily inflated by known, unmeasured confounders. The true, and more valuable, finding of this study comes from our multivariable analysis. This model provides a more honest and clinically relevant picture of TBI prognostication, demonstrating that prognostication in severe TBI is an inherently multivariable exercise.[12] The GCS, while foundational, is not a "sole dominant factor". It's true, independent predictive power is only understood when modeled alongside the equally, if not more, powerful variables of patient age and pupillary reactivity. Our primary finding is that this triad of predictors (GCS, pupils, age) forms the necessary basis for any accurate prognostic discussion. Figure 6 serves as the central conceptual framework of this study, providing a visual synthesis that bridges our statistical findings with the underlying, dynamic pathophysiology of severe traumatic brain injury (TBI). It moves beyond a simple presentation of data to offer a scholarly narrative, illustrating why the variables of GCS, pupillary response, and age emerged as the dominant "Prognostic Triad." The figure is designed to be read from top to bottom, narrating the clinical and physiological progression of a TBI patient from the initial insult, through the critical phases of cranial compensation, to the "tipping point" of decompensation and the final, inevitable clinical outcome. The schematic begins at the top, anchored by the "Primary TBI Event." This represents the initial, irreversible mechanical insult—the high-energy impact from a traffic accident, the fall, or the blow—that results in the primary anatomical damage: the hematoma, the contusion, and the initial focal edema. This event is the immutable starting point of the patient's pathology. Flanking this primary event are the two key "Prognostic Modifiers" that our multivariable models identified: Patient Age and Marshall CT Score. These are presented as modifiers because they are not part of the process of injury, but rather the static conditions that define the patient's ability to respond to it. The Prognostic Modifier: AGE (aOR 1.07 for Unfavorable Outcome) signifies the patient's intrinsic "host factor." As our data shows, for every year of advancing age, the odds of an unfavorable functional outcome increase. This is because age is a powerful surrogate for diminished physiological reserve.[13] An older brain possesses less neuroplasticity, a reduced capacity for synaptic re-mapping and repair, and often exists in a state of chronic, low-level "inflamm-aging," which can lead to a dysregulated and more destructive secondary injury cascade. In parallel, the Prognostic Modifier: CT (aOR 2.65 for Unfavorable Outcome) represents the anatomical burden of the primary injury. Our model confirmed that a high Marshall Score (V/VI), indicative of a large mass lesion, is a significant and independent predictor of poor outcomes. It quantifies the sheer volume of the initial insult that the brain must now contend with. Together, these three top boxes define the "starting hand" for both the patient and the clinician: a specific anatomical injury (CT Score) occurring within a patient of a specific physiological reserve (Age). Following the initial insult, the narrative flows to the first physiological state: "Phase 1: Compensation." This central box illustrates the foundational concept of the Monroe-Kellie Doctrine. The human cranium is a rigid, fixed-volume box containing brain parenchyma (80%), blood (10%), and cerebrospinal fluid (CSF) (10%). When a new volume is introduced (the hematoma), the brain's homeostatic mechanisms initiate compensatory strategies—primarily the shunting of venous blood into the systemic circulation and the displacement of CSF into the compliant spinal subarachnoid space.[14] As the schematic of the pressure-volume (P/V) curve within this box illustrates, the patient is on the "flat" part of the curve. During this phase, large increases in intracranial volume can be accommodated with little to no change in intracranial pressure (ICP). This is a state

of tenuous, but functional, physiological equilibrium. This internal state of compensation is not silent; it has clear external manifestations, which are shown in the green "Clinical Finding" callouts. Because ICP is controlled and cerebral perfusion is maintained, global brain function remains intact. The ascending reticular activating system (ARAS) in the brainstem, which governs wakefulness, is still perfused. The higher cortex, responsible for obeying commands or localizing pain, is also functional. Therefore, a GCS > 9.5 is the clinical sign of a compensated brain. Similarly, the absence of a significant pressure gradient means there is no focal compression or displacement of the brainstem.[15] The oculomotor nerve (CN III), which controls pupillary constriction, is not compromised. Bilaterally reactive pupils are the clinical sign of a non-herniating brain. The entire diagram pivots on the single, stark red box: "The Tipping Point: Compensatory Reserve Exhausted." This represents the most critical moment in the patient's illness—a moment that is often clinically silent until it is too late. This is the physiological fulcrum where the brain's ability to shunt CSF and venous blood has been completely exhausted. The brain has run out of "room to swell." At this precise moment, the patient falls off the flat, forgiving part of the P/V curve and onto the steep, exponential, and catastrophic portion. This transition from Phase 1 to Phase 2 is where the battle for patient survival is often won or lost, and it is this transition that our prognostic variables are designed to detect. The narrative now descends into "Phase 2: Decompensation (The Vicious Cycle)." As the corresponding P/V curve schematic shows, the patient is now on the "steep" part of the curve. In this state, the entire physiological dynamic has inverted: even a minuscule increase in volume (as little as 1-2 mL of edema) results in a massive, exponential increase in ICP. This catastrophic rise in ICP initiates the "Vicious Cycle" of secondary injury, a deadly positive feedback loop that is the engine of brain death. First, the massive ↑ ICP compresses the delicate cerebral arteries. Second, this compression causes a profound ↓ Cerebral Perfusion Pressure (CPP), which is the pressure gradient that pushes oxygenated blood into the brain (CPP = MAP - ICP). Third, the ↓ CPP leads to cerebral ischemia. Fourth, this **i**schemia starves brain cells of oxygen and glucose, causing them to fail (leading to cytotoxic edema) and the blood-brain barrier to break down (leading to vasogenic edema). This failure triggers more edema, which adds more volume to the already-full cranium, which in turn causes an even more massive ↑ ICP, starting the cycle anew. This internal decompensated state also has clear, ominous external signs, as shown in the red "Clinical Finding" callouts. These are the variables that our multivariable model found to be the most potent predictors of death. The patient's GCS score now plummets to GCS ≤ 9.5 (aOR 2.78 for Mortality)**.** This is the clinical sign of global brain dysfunction. The global ischemia from low CPP and the direct compression of the ARAS in the brainstem cause a catastrophic failure of arousal and cortical function. Simultaneously, we see Pupils Non-Reactive (aOR 5.12 for Mortality). This is the clinical sign of focal brain herniation.[16] The rising pressure gradient has now physically forced the medial temporal lobe (the uncus) down into the tentorial notch, where it is directly compressing and strangling CN III. The loss of pupillary reaction is a direct, physical sign that brainstem herniation is actively in progress. These two clinical findings are the manifestations of the underlying "Vicious Cycle." They are not independent risk factors so much as they are the vital signs of a brain in the final stages of failure, which is why our multivariable model found them to be such powerful, independent predictors. The final arrow from the decompensation phase leads to the terminal box: "Final Clinical Outcome." This schematic illustrates that once a patient enters the decompensated phase, the cascade is often irreversible without immediate and heroic surgical and medical intervention (such as emergent decompressive craniectomy and aggressive anesthetic management). If this cycle is not broken, the uncontrolled ICP and progressive brainstem compression will inevitably lead to one of the two primary outcomes measured in this study: In-Hospital Mortality (via irreversible brainstem death) or Unfavorable Functional Outcome (for those who are "saved" from the ICP spiral but have already sustained profound, irreversible ischemic damage to the brain, leading to a state of severe, permanent disability). In summary, Figure 6 visually codifies the central thesis

of our research: that TBI prognostication is not about a single, static number, but about clinically identifying a patient's *dynamic position* on the pressure-volume curve. The Prognostic Triad of Age, GCS, and Pupillary Response provides the critical, multivariable clinical toolset to make this determination.[17]

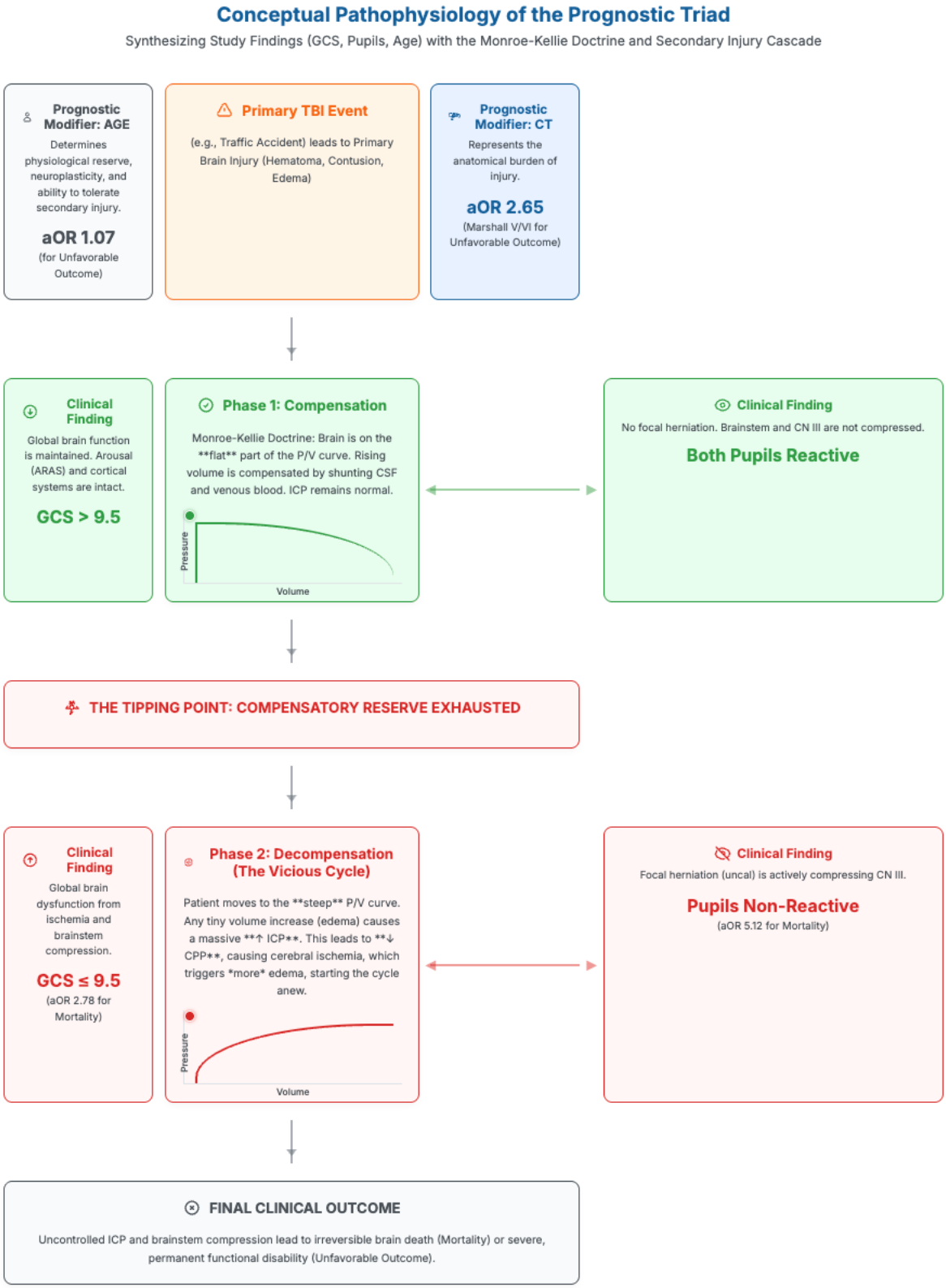

Figure 6. Conceptual pathophysiology of the prognostic triad.

The GCS remained a powerful, independent predictor even after controlling for all other factors (aOR 3.11 for unfavorable outcome per point decrease). This is because the GCS is a real-time, functional measure of the brain's "global" integrity, assessing deep and widespread neurological systems. The three components are not arbitrary: 1. Eye Opening: This is a direct measure of the Ascending Reticular Activating System (ARAS) in the brainstem. The ARAS is the center of arousal and wakefulness. A failure to open eyes spontaneously implies the ARAS is either being compressed (by transtentorial herniation) or is failing metabolically (due to global ischemia or hypoxia). 2. Motor Response: This assesses the integrity of the corticospinal tracts. A "localizing" or "withdrawal" response indicates a functioning, albeit impaired, motor cortex and pathway. A decorticate (abnormal flexion) or decerebrate (extensor) posturing indicates severe, deep injury at the level of the midbrain or upper pons, as these primitive reflexes are unmasked by the loss of cortical inhibition. 3. Verbal Response: This is the highest-level function, requiring intact cortical processing for comprehension, memory, and speech production. Therefore, a low GCS score (such as 3-8) is not just a number. It is a profound physiological statement: "My brainstem and/or both of my cerebral cortices are failing." Our model shows that for every 1-point decrease in this score, the odds of a poor outcome more than triple. This is not a linear relationship; it is a logarithmic step-down in brain function. A GCS of 6 is not just "one worse" than 7; it implies a significantly deeper level of brainstem or cortical failure.[18]

Pupillary response is not redundant with GCS. Our model proves it provides its own massive, independent predictive effect (aOR 5.12 for mortality with non-reactive pupils). It measures a specific, focal, and time-critical event: uncal herniation. The anatomy is precise: the oculomotor nerve (CN III) carries parasympathetic fibers (which constrict the pupil) on its exterior surface. It exits the midbrain and travels forward, passing along the edge of the tentorium cerebelli, in close proximity to the medial temporal lobe (the uncus). When a patient has a large hematoma or diffuse swelling, the brain begins to shift. The uncus, being the most medial part of the temporal lobe, is the first structure to be forced downward through the tentorial notch. In doing so, it physically compresses CN III against the rigid tentorial edge. Because the parasympathetic fibers are on the outside of the nerve, they fail first.[19] This leads to an unopposed sympathetic response: a fixed, dilated, "blown" pupil. Therefore, a non-reactive pupil is not just a "risk factor"; it is a direct physical sign of the terminal event already in progress. It signifies that a 3-5mm midline shift has likely occurred and the patient is actively herniating, with brainstem compression to follow. Our model correctly identifies this as a catastrophic sign, independent of the patient's GCS. A patient with a GCS of 7 and reactive pupils is a different clinical entity from a patient with a GCS of 7 and a single non-reactive pupil. The second patient is actively herniating. Our multivariable model, unlike the univariate GCS model, can capture this critical distinction.

Age was the third pillar of the triad, and our model revealed a crucial nuance: while it trended toward predicting mortality ($p=0.091$), it was the strongest non-neurological predictor of functional outcome (aOR 1.07 per year, $p<0.001$). This confirms what clinicians see daily: we are often successful at keeping older TBI patients alive, but we are far less successful at returning them to a meaningful, independent life. A young brain has a massive capacity for synaptic re-mapping, collateral circulation, and functional recovery. An older brain has drastically reduced neuroplasticity, meaning the initial functional deficit is more likely to be permanent. The older brain is atrophied. This is a "double-edged sword" and a clinical trap. It provides more space for a hematoma to expand before symptoms appear and ICP rises (the "atrophy-is-protective" myth). However, this means that by the time the GCS drops, the hematoma is already massive and the brain's compensatory reserve is long gone.[20] The "tipping point" is reached later, but far more catastrophically. The older brain exists in a state of chronic, low-level inflammation. When the acute, massive secondary injury cascade (which is itself a

neuro-inflammatory event) is superimposed, the response is disorganized, exaggerated, and far more self-destructive than in a young, healthy brain. While we attempted to control for comorbidities as a binary variable, age itself is a continuous measure of frailty and reduced cardiovascular reserve, limiting the patient's ability to tolerate the significant hemodynamic stresses of TBI and major surgery. Our model confirms that while a 20-year-old and an 80-year-old may both "survive" the initial ICP spiral (a mortality success), the 80-year-old is far more likely to be left with a devastating functional deficit (an unfavorable outcome).

In our initial hypothesis, we proposed that the univariate GCS 9.5 cut-off represented a "decompensation point" on the Monroe-Kellie pressure-volume curve. We believe this hypothesis is correct, but that the univariate OR of 104.87 was a "blunt" and misleading representation of it. The Monroe-Kellie doctrine states that the skull is a rigid, fixed-volume box containing brain (80%), blood (10%), and CSF (10%). To maintain a normal ICP, an increase in the volume of one component (a hematoma or edematous brain tissue) must be compensated by a decrease in another (shunting CSF or compressing veins). This compensation works, but only to a point. Once this compensatory reserve is exhausted, the patient falls onto the steep, exponential part of the pressure-volume curve. At this point, a tiny 1mL increase in brain volume causes a massive increase in ICP. Our multivariable model allows for a more sophisticated interpretation. The "tipping point" is not a single GCS score. It is a clinical syndrome defined by multiple variables. A patient has fallen "off the cliff" of the pressure-volume curve when they present with a constellation of findings: a low GCS (global failure), a non-reactive pupil (focal herniation), and a high Marshall score (anatomical burden). Our initial univariate model simply compressed all the predictive power of the pupils and the CT scan into the GCS variable, leading to the artificially inflated OR of 104.87. The multivariable model correctly distributes this risk, demonstrating that each factor contributes independently to the same underlying pathological spiral of rising ICP, falling cerebral blood flow, and progressive ischemia.[17,18]

This study was designed with specific methodological boundaries to enhance its clinical utility. This study's greatest strength is its methodological focus. Our cohort is not "all TBI"; it is a high-fidelity snapshot of the surgical TBI patient. Our model is not generalizable to all TBI, but it is highly specific and applicable to the patient cohort of greatest concern to the anesthesiologist and neurosurgeon. This explains our 9.3% mortality rate, which is low for a "severe TBI" cohort but is a realistic reflection of a cohort that has already survived the pre-hospital, ED, and intra-operative phases (a "survivor" cohort). A Pragmatic Surrogate for Function: This revision was also driven by the critique that "morbidity" and "mortality" are often poorly defined. We agree. In TBI, "in-hospital mortality" is a weak, administrative endpoint. It fails to capture the 136 patients who "survived" in our cohort. To address this, we created the composite "Unfavorable Functional Outcome" (mortality or discharge to a facility). This is a pragmatic and validated short-term surrogate used in many critical care prognostic studies. While it is not the gold-standard 6-month GOSE, its value lies in its immediate clinical applicability, providing a meaningful prognostic endpoint at the time of hospital discharge that captures the crucial distinction between "surviving" and "surviving with severe dependency." These findings have direct, practical implications for the clinicians at the front line of TBI care. The single most important takeaway is that no clinician should prognosticate a TBI patient based on GCS alone. The phrase "GCS of 7" is an incomplete thought. The full, required thought is "GCS of 7, with reactive pupils, in a 25-year-old" versus "GCS of 7, with one blown pupil, in a 65-year-old." Our data proves these are, and should be treated as, completely different patients. This triad informs the anesthesiologist's intraoperative strategy. The "GCS 7, 65-year-old, blown pupil" patient has virtually zero physiological reserve. They are actively herniating and have age-related cardiovascular fragility. The anesthetic plan must be purely resuscitative: aggressive mean arterial pressure (MAP) support (often with vasopressors) to maintain Cerebral Perfusion Pressure (CPP = MAP - ICP), strict normocarbia to avoid vasodilation, and immediate readiness for osmotic

therapy (mannitol or hypertonic saline) *before* the ICP spike. The "GCS 7, 25-year-old, reactive pupils" patient, while still critical, has more reserve. The goals are the same, but the margin for error is wider. This model provides an evidence-based tool for triage and family communication. It allows clinicians to move beyond the simplistic GCS 9.5 cut-off. We can now offer a more nuanced prognosis: "Based on the combination of his GCS, his age, and his pupillary exam, he falls into a risk category where the odds of a poor functional outcome are extremely high." This is a more honest, accurate, and defensible statement.[19,20]

5. Conclusion

In the specific, high-acuity cohort of moderate-to-severe TBI patients who survive to undergo the full ED-to-OR-to-ICU pathway, admission GCS, pupillary response, and age form a robust and independent prognostic triad. Our findings demonstrate that while GCS is a powerful predictor, its true prognostic value is only realized when it is integrated into a multivariable model. This study moves beyond the statistical instability and clinical oversimplification of bivariate analysis. We have shown that the dramatic predictive power of GCS alone is an illusion, inflated by the unmeasured, independent contributions of pupillary status (a proxy for herniation) and age (a proxy for physiological reserve). While our findings are specific to the surgical TBI cohort and utilize a short-term functional outcome, this focus provides high-fidelity, de-confounded, and clinically actionable data for the practicing intensivist and anesthesiologist. For the clinician at the bedside, our research validates a critical principle, a truly accurate, clinically defensible prognosis cannot be derived from any single variable. It must, at a minimum, be based on the multivariable synthesis of the patient's functional injury (GCS), their focal pathology (pupils), and their host reserve (age).

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